



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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AUG 12 1998

Jeffrey N. Gibbs, Esq.
Hyman, Phelps & McNamara, P.C.
700 Thirteenth St. N.W.
Suite 1200
Washington, DC 20005

Re: 92P-0405

Dear Mr. Gibbs:

This letter is in response to the citizen petition submitted by you to the Food and Drug Administration (FDA) on October 22, 1992, and the supplement thereto filed on December 2, 1992. FDA apologizes for not answering your citizen petition sooner. At the time FDA received your citizen petition, FDA believed that it would respond to the petition after it considered the comments on the draft Compliance Policy Guide (CPG) "Commercialization of Unapproved In Vitro Diagnostic Devices (IVD's) Labeled for Research and Investigation" and revised the draft. Upon further consideration of FDA's regulation of commercialized homebrew or other in vitro diagnostics and comments received, FDA believed it would be better to clarify some of the regulation of IVD issues through notice and comment rulemaking in the Analyte Specific Reagent (ASR) rulemaking (62 FR 62243, November 21, 1997). FDA then published a revised draft of the "Commercialization of In Vitro Diagnostic Devices (IVD's) Labeled for Research Use Only or Investigational Use Only." (63 FR 235, January 5, 1998) (IVD CPG) for public comment. This guidance document represents the agency's current thinking on commercialization of in vitro diagnostic devices labeled for research use only or investigational use only. Finally, FDA published the classification/reclassification of Immunohistochemistry Reagents and Kits (IHC) final rule (63 FR 30132, June 3, 1998). With these publications elucidating FDA's regulation of in vitro diagnostics as medical devices, FDA now believes that it can issue a fully responsive answer to your citizen petition.

FDA has reviewed your citizen petition and supplement, and has decided to deny the petition. FDA concludes, consistent with the Analyte Specific Reagents final rule, the Immunohistochemistry Reagents and Kit final rule, and the IVD CPG, therefore:

- (1) the Commissioner of Food and Drugs may regulate assays developed by clinical reference laboratories strictly for in-house use as medical devices;
- (2) FDA has the authority to provide guidance to industry and issue a final CPG addressing or referring to in-house assays;

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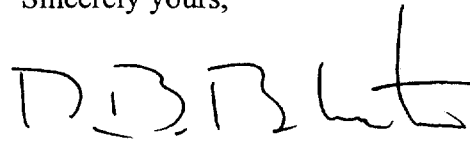
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(3) the Compliance Policy Guide (CPG) entitled "Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research or Investigation," may assert that FDA has the authority to regulate "home brew" assays; and

(4) any CPG issued by FDA on the distribution of in vitro diagnostic devices labeled for research or investigation, may address assays developed by clinical reference laboratories for in-house purposes.

Sincerely yours,

A handwritten signature in black ink, appearing to read "D. B. Burlington". The signature is stylized with a large, looped "B" and a long, horizontal stroke at the end.

D. Bruce Burlington, M.D
Director
Center for Devices and
Radiological Health

Enclosure

Enclosure Re: 92P-0405

Hyman, Phelps & McNamara submitted a citizen petition to the Food and Drug Administration (FDA) on October 22, 1992, and a supplement thereto filed on December 2, 1992.

Hyman, Phelps & McNamara's petition requests the following actions:

- “(1) that the Commissioner of Food and Drugs not regulate as medical devices assays developed by clinical reference laboratories strictly for in-house use;
- (2) that no final CPG addressing or referring to in-house assays be issued; and
- (3) that the Compliance Policy Guide (CPG) not assert that FDA has the authority to regulate “home-brew” assays, even if the CPG also disclaims any intent to exercise this alleged authority.”

The supplement to Hyman, Phelps & McNamara's petition further requests:

- “that any final CPG issued by FDA on the distribution of research and investigation *in vitro* diagnostics, as well as any other CPG or similar document, exclude assays developed by clinical reference laboratories for in-house purposes, whether developed from components or from commercially available kits.”

FDA reviewed Hyman, Phelps & McNamara's citizen petition and supplement, and decided to deny the petition for the reasons discussed below.

BACKGROUND

In recent years, more sophisticated clinical laboratories have begun to develop and prepare in-house *in vitro* diagnostic tests from components or from commercially available kits. Using ingredients that they frequently purchase from biological or chemical suppliers, clinical laboratories have developed a wide variety of in-house tests (sometimes called “home brew” tests) for use in the diagnosis of infectious diseases, cancer, and genetic and various other conditions. FDA currently regulates the safety and effectiveness of diagnostic tests that are manufactured and commercially marketed as finished products. However, “home brew” tests have not been actively regulated by FDA and the ingredients used in them generally are not produced under FDA assured manufacturing and quality system regulations. Other general controls also have not been applied routinely to these products. The laboratories producing such in-house tests and offering the tests as laboratory services are currently regulated by the Health Care Financing Administration (HCFA) under the Clinical Laboratory Improvement Amendments of 1988 (Pub. Law 100-578 (1988)) (CLIA) for compliance with general laboratory standards regarding personnel, proficiency testing, quality control, and quality assurance.

In an effort to address FDA concerns about the lack of product controls for *in vitro* diagnostic devices, the Center for Devices and Radiological Health (CDRH) released a draft CPG entitled, “Commercialization of Unapproved *In Vitro* Diagnostic Devices Labeled for Research and Investigation” on August 3, 1992, and invited comments from interested persons. The draft CPG addressed the commercialization of unapproved *in vitro* diagnostic devices labeled for research or investigational use, that are actually used for the diagnosis or management of disease or other

conditions in humans. Hyman, Phelps & McNamara responded by submitting a Citizen Petition concerning the CPG dated October 22, 1992. Shortly after Hyman, Phelps & McNamara submitted Hyman, Phelps & McNamara's citizen petition, Hyman, Phelps & McNamara received a revised, undated draft CPG for comment. On December 2, 1992, Hyman, Phelps & McNamara submitted a supplement to Hyman, Phelps & McNamara's original citizen petition commenting on the revised draft CPG.

On November 21, 1997, FDA published a final rule (62 FR 62243), the ASR rule, in which FDA set forth an approach to regulating these in-house tests intended to diagnose various medical conditions. The ingredients and other materials used in developing these tests may be divided into two groups. The first group is referred to as general purpose reagents, which include the laboratory apparatus, collection systems, and chemicals used broadly in a wide variety of tests. The second group is composed of chemicals or antibodies that may be thought of as the "active ingredients" of a test and which are useful only in testing for one specific disease or condition. It is this group of active ingredients or analyte specific reagents (ASR) that FDA is proposing to regulate. FDA identifies ASR's as antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar biological reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens. FDA's primary goals in this rulemaking proceeding are to assure that ASR's are high quality reagents and that performance claims are restricted to those made by the final test developer. FDA also seeks to ensure a higher and more appropriate level of regulatory

review for those ASR's whose use present a particularly high risk to public health. FDA classifying or reclassifying low risk ASR's into class I, and to exempt the class I ASR's from the premarket notification requirements. FDA is also designating all ASR's as restricted devices and to establish restrictions on their sale, distribution and labeling. FDA is retaining two ASR's used in blood banking tests as class II ASR's. In addition, FDA classifying or retaining high risk ASR's in class III.

FDA published a final rule (63 FR 30132; June 3, 1998) to classify/reclassify IHC's into three classes depending on intended use. IHC's concern the diagnostic laboratory practice that combines immunologic techniques, using specially prepared antibody reagents, with the examination of intact cells and tissues under the microscope by a pathologist or other trained laboratory scientist. FDA's primary goal in this rulemaking was to reclassify most IHC's based on their intended use and to lessen the regulatory burden for bringing IHC's to market. Most IHC's are now classified/reclassified as class I or II. The final rule also reinforces the point that IHC's used for diagnostic purposes has been and will continue to be subject to good manufacturing practices.

On January 5, 1998, FDA made available a draft Compliance Policy Guide (CPG) entitled "Commercialization of In Vitro Diagnostic Devices (IVD's) Labeled for Research Use Only or Investigational Use Only." The purpose of the CPG is to provide guidance on FDA's enforcement priorities concerning investigational or research in vitro products that are being commercialized for diagnostic or prognostic purposes.

PETITIONER'S STATEMENT OF GROUNDS

The Citizen Petition and Supplement states five grounds on which Hyman, Phelps & McNamara rely:

1. The final rule promulgated to implement the CLIA Amendments of 1988 (42 CFR Part 493) makes clear that FDA does not have jurisdiction to regulate test systems, assays, or examinations that are not commercially available.
2. FDA lacks the statutory authority to regulate in-house assays because FDA's approval requirements apply only to medical devices that are placed in commercial distribution.
3. FDA cannot regulate in-house laboratory assays unless the agency first conducts notice and comment rulemaking under the terms of the Administrative Procedure Act (APA) (5 U.S.C. 553).
4. The regulation of in-house laboratory assays as medical devices would have the perverse effect of diminishing public health.

Consequently, the petition requests that the Commissioner of Food and Drugs not regulate as medical devices assays developed by clinical reference laboratories strictly for in-house use.

DISCUSSION

A. CONSISTENCY WITH CLIA

Hyman, Phelps & McNamara contend that CLIA provides adequate safeguards for patients and that the final rule implementing the 1988 amendments to CLIA (42 CFR Part 493) clearly does not contemplate regulation of in-house assays by FDA.

Both HCFA and FDA have jurisdiction over in-house assays. The regulation of in-house assays by FDA is consistent with CLIA. HCFA regulates laboratory services under CLIA. FDA regulates products as a drug, biologic or device under Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 *et seq.*) (FDCA), Safe Medical Devices Act of 1990 (Pub. L. 101-629) (SMDA) and other statutes. Currently HCFA regulates in-house assays as a laboratory service for compliance with general laboratory standards regarding personnel, proficiency testing, quality control, and quality assurance. However, HCFA regulations do not include the same product controls found in FDA regulations. HCFA's regulation of laboratory services under CLIA does not address FDA's concern that the ingredients of the home-brew tests are essentially unregulated and therefore of unpredictable quality.

Accordingly, in conjunction with HCFA's regulation of laboratory services under CLIA, FDA will regulate ASR's, an ingredient of in-house assays, as a device with the product controls delineated in the rule concerning ASR's. The rule delineates a regulatory scheme that attempts to assure that the active ingredients of in-house assays are high quality reagents and that performance claims are restricted to those made by the final test developer. FDA's regulation of ASR's includes: (1) Placing the majority of ASR's into class I and exempting them from premarket notification requirements; (2) maintaining other general controls, including registration, listing,

and compliance with current good manufacturing practice (CGMP) and medical device reporting (MDR) requirements; and (3) restrictions on the sale, distribution or use of these devices. In addition, FDA will make a small number of ASR's presenting a higher risk to public health class II or III devices.

B. STATUTORY AUTHORITY OF FDA TO REGULATE IN-HOUSE ASSAYS

Hyman, Phelps & McNamara argue that FDA lacks the statutory authority to regulate in-house assays because FDA's approval requirements apply only to medical devices that are introduced or delivered for introduction into interstate commerce for commercial distribution. Hyman, Phelps & McNamara dispute that in-house assays are medical devices, rather Hyman, Phelps & McNamara opine that they are services. Hyman, Phelps & McNamara also contend that FDA lacks statutory authority to regulate in-house assays that are created and used at one site.

Hyman, Phelps & McNamara's assertion that an in-house assay system or method is not a device within the meaning of the FDCA is without merit. Section 201(h) of the FDCA defines medical devices to include *in vitro* reagents (21 U.S.C. 321(h)). The regulations define *in vitro* diagnostics to be "those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions" (21 CFR 809.3(a)). Clearly section 809.39(a) includes ASR's because it uses a reagent to diagnose a disease. Any in-house assay, test, or system which is a diagnostic test produced using an ASR falls within the definition of device as delineated in the FDCA and its regulations. Therefore, in-house assays are a medical device under FDCA.

In addition, Hyman, Phelps & McNamara's argument that FDA lacks statutory authority to regulate in-house assays is unpersuasive. Section 709 of the FDCA (21 U.S.C. 379a) establishes that "[i]n any action to enforce the requirements of this Act respecting a device the connection with interstate commerce required for jurisdiction in such action shall be presumed to exist." In addition, a number of courts have established the interstate commerce nexus by a showing that one or more ingredients used in the manufacture of a product have crossed state lines. (Baker v. United States 932 F2d 813, 814-5 (9th Cir. 1991); United States v. Article of Food . . . Coco Rico, Inc., 752 F2d 11,14 (1st Cir. 1985); United States v. Dianovin Pharmaceuticals, Inc., 475 F2d 100, 103 (1st Cir.), cert. denied 414 U.S. 830 (1973)) In finding the interstate commerce nexus requirement satisfied even when only an ingredient is transported interstate, the courts have been guided by Supreme Court statements on basic principles in interpreting the FDCA. The Supreme Court has noted that it believes "Congress fully intended that the [FDCA's] coverage be as broad as its literal language indicates" (United States v. Bacto-Unidisk, 89 S.Ct. 1410, 1418 (1969)), and that courts should hesitate to create "loopholes" that have no basis in statutory language (Kordel v. United States 69 S.Ct. 106 (1948)). Manufacturers of ASR's should look at the transportation of the ingredients of the ASR as well as the ASR itself to determine the existence of the interstate commerce nexus. Hyman, Phelps & McNamara argue that an interstate commerce for commercial distribution nexus cannot be established if an in-house assay is created and used at one site. Hyman, Phelps & McNamara's argument discusses whether the final product is in interstate commerce for commercial distribution but fails to address whether the ingredients were in interstate commerce. Consequently, Hyman, Phelps & McNamara's interstate commerce for commercial distribution argument is unpersuasive and insufficient to rebut the

presumption.

C. APA REQUIRES NOTICE AND COMMENT RULEMAKING

Hyman, Phelps & McNamara argue that the CPG would violate the APA because the CPG represents a substantive change in FDA's regulation of in-house assays which makes the CPG subject to the APA's rulemaking requirements. Hyman, Phelps & McNamara contend that the casual note attached to the draft CPG was not adequate notice under the APA because it was not calculated to solicit maximum public participation and the response period was not adequate. Moreover, Hyman, Phelps & McNamara add that FDA needs to perform a threshold assessment to determine whether a regulatory impact analysis or regulatory flexibility analysis is necessary as required by Executive Order 12291 or the Regulatory Flexibility Act (5 U.S.C. 601-612).

In the draft CPG FDA intended to provide assistance to the regulated industry in its efforts to comply with the requirements of the applicable laws and implementing regulations. Guidance documents are intended to assist industry by clarifying statutory and regulatory requirements. An equally important purpose for guidance is to help ensure that FDA's employees implement FDA's mandate in a fair and consistent manner. FDA agrees that public participation generally benefits the guidance document development process. In response to a citizen petition concerning issues relating to FDA's development and use of guidance documents, FDA published a notice on its guidance document procedures on February 27, 1997 (62 FR 8961).

However, FDA does not treat guidance documents that set forth FDA's general policies and interpretations of laws or regulations as binding. The APA does not require notice-and-comment rulemaking for such policy statements as guidance documents (American Bus Association v. United States 627 F2d 525 (1980); Community Nutrition Institute v. Young 818 F2d 943 (1987); and Alaska v. United States Dept. Of Transportation 868 F2d 441 (1989)). Consequently, the draft CPG does not violate the APA. As a result, FDA consideration of whether the regulation of in-house assays is a substantive rule, whether the note provides adequate notice under the APA, or whether a regulatory impact analysis or regulatory flexibility analysis is necessary is moot.

D. EFFECT ON PUBLIC HEALTH

Hyman, Phelps & McNamara argue that the proposed CPG may diminish the quality of health care because FDA might not have approved a kit for a specific analyte on the market and therefore patients would be without an assay for an analyte whose detection might be medically useful.

FDA recognizes the clinical importance of in-house developed testing as a mechanism for providing novel, highly specialized tests in a relatively short time, sometimes for diseases that affect a relatively small proportion of the population. However, FDA needs to balance this concern against its concern about the lack of product controls. Currently, the ingredients of the in-house developed tests are essentially unregulated and therefore of unpredictable quality. Neither patients nor practitioners are assured that all ingredients in the in-house tests are capable

of producing consistent results when ingredients are of unpredictable quality. These in-house tests are currently being used in the diagnosis of infectious diseases, cancer, and genetic and various other conditions. FDA's rule on ASR's is an attempt to reach an appropriate compromise between the competing concerns.

CONCLUSION

The requests in Hyman, Phelps & McNamara's petition are denied. For the reasons discussed above, FDA concludes that consistent with the Analyte Specific Reagents final rule: (1) the Commissioner of Food and Drugs may regulate assays developed by clinical reference laboratories strictly for in-house use as medical devices; (2) FDA has the authority to provide guidance to industry and issue a final CPG addressing or referring to in-house assays; (3) the CPG entitled "Commercialization of Unapproved *In Vitro* Diagnostic Devices Labeled for Research and Investigation" may assert that FDA has the authority to regulate "home brew" assays; and (4) any CPG issued by FDA on the distribution of *in vitro* diagnostic devices labeled for research or investigation, may address assays developed by clinical reference laboratories for in-house purposes.